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Limits to the Use of the Procalcitonin Level as a Diagnostic Marker

SIR—The comparison by Simon et al. [1] of the accuracy of serum C-reactive protein levels and procalcitonin levels for the diagnosis of bacterial infections is most interesting. Three important points, however, merit comment.

First, with regard to the source of procalcitonin, recent findings have revealed that, in marked inflammation, and especially in systemic infection [2], the calcitonin *(CT)* gene is ubiquitously expressed in *parenchymal* cells. Thus, the expression of the *CT* gene is not limited to liver or leukocyte cells. Furthermore, in leukocytes, *CT* gene expression is only very limited and transient [3]. No *CT* gene expression is found if these cells are harvested from patients who have sepsis and markedly elevated serum procalcitonin levels. In whole blood, lipopolysaccharide stimulation is unable to induce any detectable procalcitonin production by leukocytes. Moreover, the observation that some patients with sepsis have high serum procalcitonin levels even after near-complete eradication of their leukocyte population by chemotherapy suggests that these cells are not a major source of procalcitonin. Parenchymal cells (including liver, kidney, and muscle cells and adipocytes) constitute the largest mass of tissue and the principal source of circulating procalcitonin in patients with sepsis [4]. Procalcitonin, a prototype of *hormokine* mediators, can follow either a classical hormonal expression pathway or, alternatively, a cytokine-like expression pathway. The ubiquitous production of this hormokine is triggered by microbial toxins (e.g., lipopolysaccharides) together with mediators from humoral or cell-mediated host responses (e.g. IL-1b and TNF-α). These findings are relevant, as they are the basis for the superior diagnostic accuracy of procalcitonin levels, compared with C-reactive protein levels, as is shown in the excellent meta-analysis of Simon et al. [1].

Second, for the appropriate use of a marker in a clinical setting, the *functional* assay sensitivity is more relevant than the reported detection limit. The commercially available 2-site assay (LUMItest PCT; distributed by Brahms) used by Simon et al. [1] is useful to detect markedly elevated procalcitonin levels in patients with severe systemic bacterial infection or sepsis. However, this assay has the disadvantage of relative insensitivity, with a functional detection limit of 0.5 ng/mL procalcitonin. On the basis of measurements made with an ultrasensitive research assay, a study found that 30 healthy donors had a mean procalcitonin level ($\pm$SD) of 0.03 $\pm$ 0.02 ng/mL [5]. Thus, the LUMItest assay is not sensitive enough to detect mildly or moderately elevated procalcitonin levels, which limits its diagnostic use in conditions other than overt sepsis. For research purposes, more-sensitive procalcitonin assays have been described [5].

Last, any observational study investigating the diagnostic accuracy of a given marker is biased by the choice of the "gold standard." As Simon et al. [1] correctly state, this standard does not exist with respect to infection, and thus all studies are prone to potential bias. Importantly, interventional studies in which the antimicrobial therapy is guided by the marker and the "gold standard" for diagnosis is the *outcome* have the potential to resolve this dilemma. With respect to procalcitonin levels, initial studies of lower respiratory-tract infections and meningitis have shown promising results [6, 7]. The time has arrived for investigators to conduct more intervention studies for other sites of infection, using more-sensitive procalcitonin assays to tackle the vicious cycle of antibiotic overuse and emerging multidrug resistance.

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